1632

Docket No. 48340/55793-CPA

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANTS: Sherman et al.

U.S.S.N.: 08/812,393 GROUP: 1632

FILED: March 5, 1997 EXAMINER: Wilson, M.

FOR: RECOMBINANT CONSTRUCTS ENCODING T CELL RECEPTORS SPECIFIC FOR HUMAN HLA-RESTRICTED TUMOR ANTIGENS

**********

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 18, 2003.

By: Sharon Bizokas
Sharon Bizokas

**********



Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**TRANSMITTAL LETTER**

Sir:

Transmitted herewith for filing in the above-referenced patent application are the following documents:

1. Search Report Information Disclosure Statement (4 pages) and 1449 Form (1 page);
2. References for IDS (3 references);
3. Copy of PCT Search Report;
4. Copy of EPO Search Report;
5. This transmittal letter (1 page) (x2); and
6. Return Receipt Postcard

The Commissioner is hereby authorized to charge any excess fees that may be required, or credit any overpayment to Deposit Account No. 04-1105. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Date: September 18, 2003

Kathryn A. Piffat, Ph.D.

Kathryn A. Piffat, Ph.D., Reg. No. 34,901
Intellectual Property Practice Group of
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Boston, MA 02209
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Customer No. 21874

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Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450



**SEARCH REPORT INFORMATION DISCLOSURE STATEMENT**

Sir:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications or other information submitted for consideration by the Office are listed on PTO-1449, attached hereto.

II. COPIES

a. X Submitted herewith is a legible copy of (i) each U.S and foreign patent; (ii) each publication or that portion which caused it to be listed; and (iii) all other information or that portion which caused it to be listed.

b. ___ This application relies, under 35 U.S.C. § 120, on the earlier filing date of prior application Serial No. _____ , filed on ___. The following references were submitted to, and/or cited by, the Office in the prior application (s) and, therefore, are not required to be provided in this application.

III. CONCISE EXPLANATION OF THE RELEVANCE
(check at least one box)

a. X Except as may be indicated below in (b), all of the patents, publications or other information are in the English language or were cited in an English language Search Report, a copy of which is attached hereto (concise explanation not required).

b. ___ A concise explanation of the relevance of all patents, publications or other information listed that is not in the English language is as follows:

c. X The following additional information is provided for the Examiner' consideration:

X Copy of PCT Search Report.
X Copy of EPO Search Report.
References not provided herewith have previously been Provided to the Examiner.

**FEES**

IV. THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(b)
(check one box)

a. ___ within three months of the filing date of a national application (37 C.F.R. § 1.97(b) (1]. No fee or certification is required.

b. ___ within three months of the date of entry of the national stage as set forth in §1.491 in an international application (37 C.F.R. § 1.97(b) (2). No fee or certification is required.

c. X Before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b) (3)). No fee or certification is required. In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the certification under 37 C.F.R. § 1.97(e)below, or, if no certification has been made, charge our deposit account a fee in the amount of $240.00 as required by 37 C.F.R. § 1.17(p).

V. THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(c):
(check one box)

before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c) (1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c) (2)).

a. ___ No certification; therefore, a fee in the amount of $180.00 is required by 37 C.F.R. . § 1.17(p).

or

b. X See the certification below. No fee is required.

VI. CERTIFICATION UNDER 37 C.F.R. § 1.97(e) (check only one box)

The undersigned hereby certifies that

a. ___ each item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

b. ___ no item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application or, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

c. ___ Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned certifies that each item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby certifies that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application or, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

___ Please charge Deposit Account No. 04-1105 in the amount of $180.00 for the above-indicated fee. A triplicate copy of this paper is attached.

X No fee is required.

___ The fee in the amount of $180.00 is enclosed herewith.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is requested to consider this IDS under the proper rule, with a petition if necessary, and charge the appropriate fee to Deposit Account No. **04-1105**.

Respectfully submitted,

Date: September 18, 2003

Kathryn A. Piffat, Ph.D. (Reg. No.: 34,901)
Intellectual Property Practice Group of
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Boston, Massachusetts 02209
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Customer No. 21874

| FORM PTO-1449<br><br>INFORMATION DISCLOSURE STATEMENT | ATTY DOCKET NO.<br>48340/55793-CPA | SERIAL NO.<br>08/812,393 |
|---|---|---|
| | APPLICANT(S): Sherman et al. | |
| | FILING DATE:<br>March 5, 1997 | ART UNIT:<br>1632 |



**UNITED STATES PATENT DOCUMENTS**

| EXAM. INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB CLASS | FIL. DATE IF APPR |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB CLASS | TRAN YES/NO |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |

**OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)**

| | | |
|---|---|---|
| | CA | Moritz and Groner, "A spacer region between the single chain antibody and the CD3 ζ-chain domain of chimeric T cell receptor components is required for efficient ligand binding and signaling activity", Gene Therapy, 2:539-546 (1995) |
| | CB | Disis et al., "*In Vitro* Generation of Human Cytolytic T-Cells Specific for Peptides Derived from the HER-2neu Protooncogene Protein[1]", Cancer Research, 54:1071-1076 (1994) |
| | CC | Broeren et al., Conserved nucleotide sequences at the 5' end of T cell receptor variable genes facilitate polymerase chain reaction amplification", Eur. J. Immunol., 21:569-575 (1991) |
| | CD | |
| | CE | |

| Examiner: | Date: |
|---|---|
| | |

APR 12 1999

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: KATE H. MURASHIGE
MORRISON & FOERSTER LLP
2000 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20006-1888

# PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| Date of Mailing *(day/month/year)* | 09 APR 1999 |
|---|---|
| Applicant's or agent's file reference: 313332000140 | IMPORTANT NOTIFICATION |

| International application No. | International filing date *(day/month/year)* | Priority Date *(day/month/year)* |
|---|---|---|
| PCT/US97/03611 | 05 MARCH 1997 | 05 MARCH 1996 |

Applicant
THE SCRIPPS RESEARCH INSTITUTE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of th PCT Applicant's Guide.

| Name and mailing address of the IPEA/US | Authorized officer |
|---|---|
| Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | F. PIERRE VANDERVEGT |
| Facsimile N . (703) 305-3230 | Telephone No. (703) 308-0196 |

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference 313332000140 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/US97/03611 | International filing date *(day/month/year)* 05 MARCH 1997 | Priority date *(day/month/year)* 05 MARCH 1996 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant THE SCRIPPS RESEARCH INSTITUTE | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☒ Certain defects in the international application

   VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 15 SEPTEMBER 1997 | 12 MARCH 1999 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>F. PIERRE VANDERVEGT<br>Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/03611

**I. Basis f the report**

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-13 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-21 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-12 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/03611

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 21

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 21.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/03611

**V. Reasoned statement under Article 35(2) with regard t novelty, inventive step or industrial applicability; citati ns and explanations supp rting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-8, 10-20 | YES |
| | Claims | 9 | NO |
| Inventive Step (IS) | Claims | 11-14, 20 | YES |
| | Claims | 1-10, 15-19 | NO |
| Industrial Applicability (IA) | Claims | 1-20 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS

Claim 9 lacks novelty under PCT Article 33(2) as being anticipated by Broeren et al. Broeren et al teaches a DNA sequence which encodes a murine TCR (Figure 3 in particular).

Claims 1-10 lack an inventive step under PCT Article 33(3) as being obvious over Theobold et al (Proc. Natl. Acad. Sci.(USA)92:11993-11997) in view of Broeren et al (Eur. J.Immunol. 21:569-575). Theobold et al teaches the immunization of HLA-A2.1 transgenic mice with a peptide cancer antigen in order to generate murine T cells which express a T cell receptor under the control of the human histocompatability gene. Broeren et al teaches a method and degenerate primers with which a skilled artisan could isolate and amplify any rat, mouse or human TCR. The skilled artisan would have found it obvious to isolate the murine TCRs of the cells of Theobold et al by the methods taught by Broeren et al in order to better study the structuire and features of this murine TCR under the control of a human gene product.

Claims 1-10 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Zisman et al (Eur. J.Immunol. 24:2497-2505). Zisman et al teaches the murine TCR primers of Figure 6 of the instant application (Tables 2 and 3 in particular).

Claims 15-19 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Hock et al (Nature 320:275-277). Hock et al teaches a method for transforming human cells to express a recombinant gene product and teaches that these cells can be used for treatment of patients.

Le et al, Reasing et al, LaFace et al, Wentworth et al and Man et al each teach mice which are transgenic for human HLA-A2.1 and the immunization of the transgenic mice with antigenic molecules resulting in the generation of murine T cell receptors under the (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/03611

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**The description is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof: The specification and figures disclose nucleotide and amino acid sequences which are not present in a paper sequence listing or in a computer readable form.**

**Claim 9 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The claim is written in such a manner that it seems to be intended to be a dependent claim, but reference to a base claim was inadvertanly omitted.**

**Supplemental B x**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 45/05; C12N 5/10, 15/12; C07H 21/04; C12Q 1/68
and US Cl.: 536/23.4, 23.5; 435/6, 91.41, 372.3; 424/277.1

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
control of HLA-A2.1. These teachings are all supplementary to those of Theobold et al.

Moller et al is a state of the art reference which teaches the roles of the HLA-A, B and C haplotypes in human tumor immunity.

Lustgarten et al is a reference published after the priority date of this application which teaches that some epitopes which are immunogenic in humans may not be immunogenic in transgenic mice.

Claims 11-14 and 20 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest flexible linkers to join the construct to .delta. chains or a method of identifying tumors using the engineered cells.

Claims 1-20 meet the criteria set out in PCT Article 33(4), for Industrial Applicability.

---------- NEW CITATIONS ----------

BROEREN et al. Conserved nucleotide sequences at the 5' end of T cell receptor variable genes facilitate polymerase chain reaction amplification. Eur. J. Immunol. March 1991, Vol. 21, No. 3, pages 569-575, see entire document.

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Europäisches Patentamt | European Patent Office | Office européen des brevets

Generaldirektion 2 | Directorate General 2 | Direction Générale 2

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Gates, Marie Christina Esther
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5 Dartmouth Road
Dublin 6
IRLANDE

12 MAY 2003

| Application No. | Ref. | Date |
|---|---|---|
| 97 914 916.8-2406 | PL810EP/MCG/TC | 07.05.2003 |
| Applicant: The Scripps Research Institute | | |

**Communication pursuant to Article 96(2) EPC**

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

**of 4 months**

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

**Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).**

EUROPÄISCHES PATENTAMT - EUROPEAN PATENT OFFICE - OFFICE EUROPÉEN DES BREVETS

12 MAY 2003

HEDER A G
Primary Examiner
for the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents:**

Text for the Contracting States:
AT BE CH LI DE DK ES FI FR GB GR IE IT LU MC NL PT SE

**D scription, pages:**

1-13 as originally filed

**Claims, No.:**

1-21 as originally filed

**Drawings, sheets:**

1-13 as originally filed

The present application relates to the cloning of T-cell receptors (TCR) from cytotoxic T-cells (CTL) of human HLA-A2.1-transgenic mice, said TCR being specific for a human tumour-derived antigen (TAA), said TCR further being human HLA-2-restricted, and containing variable regions of the $\alpha$ and/or $\beta$ chains of mouse TCR. The invention further relates to nucleic acid sequences coding for said TCR or parts thereof, and to the transfer of such nucleic acids to suitable host cells, e.g. peripheral blood lymphocytes (PBL) from a tumour patient.

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 - Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-7, 1995
D2 - Man et al., J. Immunology 153:4458-67, 1994
D3 - Disis et al, Cancer Res. 54:1071-6, 1994
D4 - Moritz and Groner, Gene Therapy 2:539-46, 1995
D5- Hock and Miller, Nature 320:275-7, 1986
D6 - Lustgarten et al., Human Immunology 52, 109-118 (1997)